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Application No.	Ref.	Date
00 980 850.2-1216	P705728EP-PCT/D	21.06.2002
Applicant: Pharmacia Corporation		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in three copies on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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BONZANO C
Primary Examiner
for the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)
US5518738 A1 (5 pages)
US5552160 A1 (7 pages)

Registered Letter

Atty. Docket No. 6794S/5/US/USC
Serial No. 10/031,898
Kararli, et al.
Refererence 6 of 6

Bescheid/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum / Date / Date: 21.06.2002	Blatt / Sheet / Feuille: 1	Anmelde-Nr.: / Application No.: / Demande n°: 00 980 850.2

The examination is being carried out on the following application documents:

Text for the Contracting States:
AT BE CH LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

Description, pages:

1-48 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

1. The following documents (D1-D4) are referred to in this communication. The following documents D2 and D4 are cited by the examiner (see the Guidelines, C-VI, 8.9). A copy of the documents is annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D1: WO 00 32189 A (G.D.SEARLE & CO.) 8 June 2000 (2000-06-08)
D2: US 5518738
D3: WO9918960
D4: US5552160.

2. The subject matter of claims 16-17 concerns a method of treatment of the human/animal body which is not susceptible of industrial application and which is expressly excluded from patentability (see Art. 52(4) EPC). The claims as presently worded are thus not allowable and should therefore be reformulated in a correct manner (see Guidelines C-IV, 4.2 "second medical" use claims).

3.1 The PCT applications D1, WO 00 32189 published on 8/06/2000 and indicated in the search report as a P document, claims the priority date of 30/11/1998.

It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 22, paragraph 1 or Article 39, paragraph 1 of the Co-operation Treaty has been paid. The requirements of Article 158(2) EPC are thus fulfilled.

Its content as filed is therefore considered as comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) and (4) EPC. This earlier application D1 shows celecoxib compositions having a D90 of less than about 200 microns, more particularly having a mean particle size of 1 micron (see D1, page 46, composition D). This means that necessarily a sufficient portion by weight is smaller than 1 micron. Furthermore, it is said that decreasing the particle size of celecoxib helps increasing the bioavailability, reducing the Tmax and increasing the Cmax (see D1: table 11-2d). These compositions, in the form of tablets and of flowable mass are useful for treating COX2 mediated disorders (see D1: page 4, lines 19-29; examples 13,14; page 32, lines 27-32; page 8, lines 11-21; page 47, lines 13-22; example 11-2; claim 72).

Thus, it is prejudicial to the novelty of the subject-matter of claims 1-7,11-18 of the present application insofar as the same Contracting States AT BE CH DE DK ES FI FR GB GR IT IE LI LU MC NL PT SE are designated.

3.2 The document D2 discloses liquid and solid pharmaceutical compositions containing well known selective COX2 inhibitors such as nabutemone an piroxicam. They are in a dosage form for oral administration in particles of 0.4 to 1 micron, hence a sufficient portion of them is smaller than 1 micron (see D2: claims 1,2,15; column 3, paragraphs 2-3; column 5, lines 57-column 6, line 8).

The subject-matter of claims 1-10,16-18 is therefore not new (Article 54(1) and (2) EPC).

4. Should the Applicant overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated over D3 and D4, as the present claimed subject matter, as far as novel, appears to be obvious over said documents.

Document D3, which is considered to represent the most relevant state of the art, discloses pharmaceutical compositions containing celecoxib, a well known COX2 inhibitor.

The present application differs in that the same compound, celecoxib, and other NSAID, in particular COX2 inhibitors are present in the form of microparticles having

a D90 particle size of 0.01-200 microns and a sufficient portion by weight smaller than 1 micron. This formulation helps giving a substantially higher Cmax and a substantially shorter Tmax.

The problem to be solved by the present invention may therefore be regarded as finding alternative, faster and more bioavailable pharmaceutical compositions containing a COX2 inhibitor, in particular celecoxib.

Document D4 discloses that compounds such as nabutemone and piroxicam, well known COX2 inhibitors, when administered in nanoparticles of about 0.4 microns have a more rapid onset of action, therefore a better bioavailability, and a reduced gastric irritation (see D4: claim 4; column 1, lines 60-67).

Therefore, being aware that the reduction of COX2 inhibitors particle size, in particular in nanoparticles, increases their bioavailability, and knowing that the compounds claimed, such as celecoxib, are also COX2 inhibitors, the person skilled in the art would have been inevitably led to reduce the particle size of celecoxib (well known COX2 inhibitors) in order to solve the problem posed.

Therefore, it seems that no inventive step in sense of Article 56 EPC can be acknowledged for the subject-matter of claims 1-18.

5. If all of the above raised objections can be overcome, then the attention of the Applicant is also drawn to the necessary corrections of the following points:

5.1 Present claims 1-10, 16-18 relate to compounds defined by reference to their pharmacological property, namely the selective cyclooxygenase II inhibitory activity. The claims cover all compounds having this properties, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the compound by reference to its pharmacological profile.

5.2 Present claims 1-10,16-18 relate to compounds defined (inter alia) by reference to the following parameter: COX2 inhibitory drug of low water solubility.

The use of these parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

5.3 Claims 16,18 relate to therapeutic applications which are actually not well defined. The use of the definitions "condition or disorder where treatment with cyclooxygenase-2 inhibitor is indicated", "COX-2 mediated condition or disorder" in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is pointed out that the mechanism of action of a drug cannot be considered in itself as a therapeutic application; the discovery that a substance has a particular pharmacological profile still needs to find a practical application in the form of a defined, real treatment of a pathological condition (see T241/95).

5.4 Moreover the claims cover all possible disorders where treatment with cyclooxygenase-2 inhibitor is indicated, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for none of such complications.
Consequently the claims lack support and the application lacks disclosure.

5.5 In claims 1.2, 7-10,15,18, the word "about" is vague and renders thus the scope of protection obscure. With respect to Article 84 EPC, it should be deleted.

5.6 The term "substantially" in claim 3, and the term "sufficient portion by weight of the particles" in claim 1 are vague and unclear. A claim cannot be considered clear in the sense of Article 84 EPC if it comprises an unclear technical feature (here "substantially all" and "sufficient portion by weight") for which no unequivocal generally accepted meaning exists in the relevant art. This applies all the more if the unclear feature is essential for delimiting the subject matter claimed from the prior art (see T728/98).

5.7 To meet the requirements of Rule 27(1)(b) EPC, the documents D1 as being relevant with respect to Article 54(3) (see Guidelines C. II, 4.3), D2-D4 should be identified in the description and the relevant background art disclosed therein should

be briefly discussed.

5.8 The statements "incorporated herein by reference" in the description (page 12, line 8; page 25, line 4) are irrelevant and unnecessary, and should be deleted (Rule 34(1)c).

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm.

2. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, and wherein about 25% to 100% by weight of the particles are smaller than 1 μm.

3. The composition of Claim 1 or Claim 2 wherein substantially all of the particles are smaller than 1 μm.

4. The composition of any of Claims 1 to 3 wherein the dose units are in the form of discrete solid articles.

5. The composition of Claim 4 wherein the solid articles are tablets or capsules.

6. The composition of any of Claims 1 to 3 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.

7. The composition of Claim 6 wherein the substantially homogeneous flowable mass is a liquid suspension.

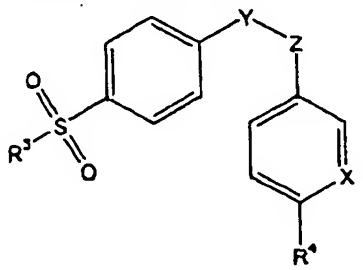
8. The composition of any of Claims 1 to 7 wherein the solid particles have a D_{25} particle size of about 450 nm to about 1000 nm.

9. The composition of any of Claims 1 to 7 wherein about 25% to 100% by weight of the solid particles have a particle size of about 450 nm to about 1000 nm.

10. The composition of any of Claims 1 to 7 wherein the solid particles have a

weight average particle size of about 450 nm to about 1000 nm.

11. The composition of any of Claims 1 to 10 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

12. The composition of Claim 11 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

13. The composition of any of Claims 1 to 10 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

14. The composition of Claim 13 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

15. The composition of Claim 14 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.

16. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering one or more dose units of a composition of any of Claims 1 to 15 one to about six times a day.

17. The method of Claim 16 wherein the medical condition or disorder is accompanied by acute pain.

18. A method of use of solid particles of a selective cyclooxygenase-2 inhibitory drug of low water solubility in manufacture of a medicament useful in treatment or prophylaxis of a COX-2 mediated condition or disorder, said solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm, and wherein about 25% to 100% by weight of the solid particles are smaller than 1 μm.